## REMARKS

Reconsideration of the Office Action mailed August 29, 2002, (hereinafter "instant Office Action") and withdrawal of the rejection of claims 18-21 and 23-45, are respectfully requested.

In the instant Office Action, claims 18-21 and 23-45 are listed as pending, and claims 18-21 and 23-45 are listed as rejected.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendments. Appendix A is captioned **"Version with markings to show changes made"**.

The Examiner has rejected claims 18-21 and 23-45 under a judicially created doctrine as allegedly being drawn to an improper Markush group, that is, the claims lack unity of invention. Applicants respectfully traverse this rejection and maintain the arguments presented in the Reply filed May 15, 2002.

The propriety of a Markush grouping is a factual issue to be decided on a case by case basis. In re Harnish, 206 U.S.P.Q. at 305. A Markush grouping is proper if the compounds in the Markush group share a single structural similarity and a community of properties (e.g., a common utility), such that the grouping is not repugnant to the principles of scientific classification. In re Harnish, 206 U.S.P.Q. at 305; Ex Parte Brouard, Leroy and Stiot, 201 U.S.P.Q. 538, 540 (P.T.O. Bd. App. 1982). The fact that the compounds in a Markush group may require different fields of search does not render the Markush group improper. Ex parte Brouard, 201 U.S.P.Q. at 540. Also, where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by consideration of the compound as a whole, and does not depend on there being a community of properties among the members of the Markush expression. Ex parte Brouard, 201 U.S.P.Q. at 305; M.P.E.P. 706.03(y).

The compounds of amended claim 18 share a common pyrazolinone nucleus that accounts for a substantial part of their molecular weight and size. In addition to the physical and chemical properties that are attributable to their structural similarity, they share a common utility as protein kinase inhibitors. Moreover, they may be prepared by common synthetic routes, as indicated on pages 122-170 of the instant specification.

In view of the above facts and legal precedents, Applicants submit that the Markush groupings of amended claim 18 are proper. Based upon the foregoing, Applicants believe that the rejection of claims 18-21 and 23-45 under the judicially created doctrine of an improper Markush group is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. 102(e) as being anticipated by Blum et al (U.S. 6,107,487) which teaches R as thiazolyl. Applicants respectfully traverse this rejection. M.P.E.P. 7.06.02(a) states, in part:

> "...for anticipation under 35 U.S.C. 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present."

In Examples 1-13 and C1-C3 of Blum, the nitrogen adjacent to the carbonyl group on the pyrazolinone ring is substituted. The substituents at this position in the Blum compounds range from methyl to substituted phenyl. Conversely, in Applicants' claim 18, the nitrogen adjacent to the carbonyl group on the pyrazolinone ring is unsubstituted. Example C4 of Blum contains an oxazole ring as its core structure, not a pyrazolinone, and therefore does not anticipate Applicants' claim 18. Based upon the foregoing, the rejection of claim 18 under 35 U.S.C. 102(e) over Blum et al. (U.S. 6,104,478) is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hiremath et al. which teaches R as benzoindolyl. Applicants respectfully traverse this rejection. In order for a reference to anticipate a claim, the reference must disclose each and every feature of the claim. The Court of Appeals for the Federal Circuit, in ruling on the standard for anticipation under 35 U.S.C. §102(b), stated

> [i]t is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice or device.
> In re Donohue, 226 U.S.P.Q. 619, 621 (1985); and "...exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference." Atlas Power Co. v. E. I. duPont DeNemours & Co., 224 U.S.P.Q. 409, 411 (1984).

Applicants' compound contains a pyrazolinone core structure. Compounds 1a-n, 4a-h, 6a-f, 7a-t, 9a-c, 10a-e, 11a-d, 12a-d and 13 a-d of Hiremath do not contain the pyrazolinone core structure.

Applicants' compound contains a carbonyl in the 4-position of the pyrzolinone and in Hiremath, compounds 2a-n contain methyl and 5a-h contain hydrogen in the 4-position. In

addition, the second nitrogen of the pyrazolinone ring in Hiremath is substituted, whereas in Applicants' compound the corresponding nitrogen is unsubstituted.

In Hiremath, compounds 3e-t, the nitrogen adjacent to the carbonyl group is substituted, whereas in Applicants' compound this nitrogen is unsubstituted. Based upon the foregoing, the rejection of claim 18 under 35 U.S.C. §102(b) over Hiremath is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. § 102(b) as allegedly being anticipated by Brick et al. which teaches R as pyrazol. Applicants respectfully traverse this rejection. Brick does not anticipate Applicants' invention because in the compounds where R is pyrazol (Dye D-4, Dye D-10 and Dye D-13), each contain a substituted phenyl group at the nitrogen in the 2-position, whereas in Applicants' compound this nitrogen is unsubstituted. Additionally, the linker in Dye D-4 and Dye D-13 contain an ethylene group, whereas Applicants' compound contains methylene as the linker. In addition, in Brick's compounds Dye D-4, Dye D-10 and Dye D-13, the nitrogen in the 5-position of the pyrazolinone ring is substituted, whereas in Applicants' compounds it is unsubstituted. Claim 18 has been amended to proviso out Dye D-3. Based upon the foregoing, the rejection of claim 18 under 35 U.S.C. §102(b) over Brick is obviated and should be withdrawn.

The Examiner has rejected claim 18 under 35 U.S.C. § 102(b) as allegedly being anticipated by Mitra et al. which teaches a benzene ring at R. Applicants respectfully traverse this rejection. Formulas I, III and VI of Mitra do not anticipate Applicants' compound because the core heterocyclic molecule of each of these formulas contains a sulfur atom, whereas Applicants' compound contains only carbon and nitrogen. Formula II does not anticipate Applicants' compound because the core molecule is a pyrrolyl, whereas Applicants' core molecule is a pyrazolinone ring. Formula IV of Mitra does not anticipate Applicants' compound because it does not have a substituted methylene group in the 4-position of the pyrazolinone group. Formula V of Mitra does not anticipate Applicants' compound because it does not contain a double bond at the carbon adjacent to the carbonyl group of the pyrazolinone ring, as Applicants' compound does.

Table 1 of Mitra lists twenty compounds of formula V and Table 2 lists twenty compounds of formula VII, the cyclopropane derivatives of the compounds in Table 1. The

compounds in Mitra's Table 2 do not anticipate Applicants' compound because of the cyclopropyl group in between the pyrazole and thiazole groups. Both tables list various possibilities for $R_1$ and $R_2$ in Mitra's compounds. At the position of Mitra's $R_2$, Applicants' compound has a hydrogen. Thus, compounds 1-10 of Table 1 and Table 2, where $R_2=C_6H_5$, do not anticipate Applicants' compound.

In compounds 11-20 of Tables 1 and 2, $R_1$ is disclosed as substituted or unsubstituted benzene. However, the carbon atom to which $R_1$ is attached is also substituted by a thioxo-thiazolidin group, whereas in Applicants' compound, the R group is attached directly to the carbon at the 5-position of the pyrazolinone ring by a double bond. There is no additional substituent. Therefore, Compounds 11-20 of Table 1 and Table 2 do not anticipate Applicants' compound.

Compounds of Formula (II) of Mitra where $R_1$ is methyl and R is as listed in compounds 11-20 of Table 2 have been provisoed out of claim 18. Based upon the foregoing, the rejection of claim 18 under 35 U.S.C. §102(b) over Mitra is obviated and should be withdrawn.

The Examiner has rejected claims 18-21 and 23-45 under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection. Applicants' response to the Examiner's enumerated points are numbered accordingly to track the Examiner's points.

iii) With respect to the term "substituted", Applicants maintain the arguments presented in the Reply filed May 15, 2002. In addition, Applicants have provided a representative list of suitable substituents on page 12, lines 12 through 25 of the instant specification. From this list, one skilled in the art could determine the scope of the term "substituted". Moreover, Applicants have disclosed numerous specific examples of substituted aliphatic, aromatic, heteroaromatic, etc. in the experimental section of the application. Applicants further submit that the definition of the term "substituted" is readily understood by one of ordinary skill in the art to include any substituent that is chemically stable when attached to the moiety that is being substituted. In addition, Applicants have provided assays to determine the activity of a particular compound. Further, even though compounds are not actually required to be made, Applicants point out that many compounds have been synthesized in support of the instant application which support the

breadth of substituents that are encompassed by the present invention. Therefore, as long as a compound is chemically stable and shows the desired inhibitory activity, it would fall within the scope of claim 18. Applicants' scope should not be hindered by a requirement to list all possible substituents.

Further, the term "substituted" is a term of art which is widely used by those skilled in the chemical and patent arts to describe compounds. Accordingly, recent US Patents have issued wtih claims that include the general term "substituted" compounds. Claim 1 of US Patent No. 6,482,842 (copy attached as Exhibit 1) reads, at column 17, lines 55-58: "...and Y is optionally substituted ethylene, alkene, alkyne, or any 2 adjacent carbon atoms of a cycloalkyl or cycloheteroalkyl ring of 3-7 atoms;". Likewise, Claim 1 of US Patent No. 6,462,036 (copy attached as Exhibit 2) reads, at column 104, lines 56-63:

> X represents a) an optionally substituted group of the formula $-(CH_2)_n-$ in which n is 1, 2 or 3, b) carbonyl, c) oxygen, d) a group of the formula $-C=NOR_{10}$, in which $R_{10}$ is a $C_{1-4}$ alkyl group, e) a group of the formula $NR_{11}$, in which $R_{11}$ is –H, an optionally substituted $C_{1-4}$ alkyl group or an optionally substituted phenyl, of f) a group of formula $S(O)_p$ in which p is 0, 1 or 2;

Thus, the rejection is inconsistent with current USPTO practice and should be withdrawn.

iv) The Examiner alleges that in claims 28-36 it is unclear what is intended to be accomplished, that Applicants have not said which protein kinase activity is inhibited and which one is not or why one would want to do that and when would this be done. The Examiner further states that it is unclear what is accomplished *in vivo* or *in vitro*. With respect to this objection, Applicants maintain the arguments presented in the Reply filed May 15, 2002. In addition, with regard to the Examiner's question as to which protein kinase activity is inhibited, Applicants respectfully direct the Examiner's attention to page 91, lines 16-24 of the instant specification, where it states:

> Compounds of this invention inhibit protein kinases from serine/threonine and tyrosine kinase classes. In particular, these compounds selectively inhibit the activity of the KDR/FLK-1/VEGFR-2 tyrosine kinases. Certain compounds of this invention also inhibit the activity of additional tyrosine kinases such as Flt-1/VEGFR-1, FGFR, PDGFR, IGF-1R, c-Met, Src-subfamily kinases such as Lck, Src, fyn, yes, etc.

Thus, it is clear which protein kinase activity is inhibited.

With respect to the Examiner's question as to why one would want to inhibit protein kinase activity, Applicants respectfully direct the Examiner's attention to page 91, lines 4-14 of the instant specification, where it states:

> It is envisaged that the disorders listed above are mediated to a significant extent by protein tyrosine kinase activity involving the KDR/VEGFR-2 and/or the Flt-1/VEGFR-1 tyrosine kinases. By inhibiting the activity of these tyrosine kinases, the progression of the disorders in inhibited because the angiogenic or vascular hyperpermeability component of the disease state is severely curtailed.

The disorders to which the above paragraph refers are the disorders listed on page 89, line 22 through page 90, line 19. Inhibiting, or slowing down the progression of these diseases would benefit the recipient of the compound in that the recipient would experience a less severe form of the disease and would expect a better quality of life and perhaps also a longer life than if the disease was left untreated.

Inhibition of kinases can be done either *in vitro*, i.e. in an assay, or *in vivo*, in a therapeutic context.

v) The Examiner alleges that in claim 29 it is unclear who the recipient is and who is not the recipient. The recipient in claim 29 is one to whom the compound of Claim 18 is administered because the recipient needs to have one or more protein kinases inhibited. Based upon the foregoing, Applicants believe that the rejection of claims 18-21 and 23-45 under 35 U.S.C. §112, second paragraph is obviated and should be withdrawn.

The Examiner has rejected claims 28-38 under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection. With respect to 35 U.S.C. §112, first paragraph, Applicants have provided a written description of the invention at *inter alia* pages 11-95 of the instant specification. Applicants have shown how to make and use the invention in Pharmaceutical Formulation section on pages 95-104 and in the Experimental section on pages 108-170 of the instant specification. Within the instant specification Applicants have also set forth the best mode of carrying out the invention.

The Examiner alleges that in claim 37 Applicants state that any and all hyperproliferative disorders are intended and regarding claim 38, that any and all angiogenesis is intended. The

Examiner further alleges that the instant specification does not provide enablement for the treatment of any and all hyperproliferative disorders and any and all angiogenesis. Applicants respectfully traverse this rejection. Hyperproliferation and angiogenesis are mechanisms which are observed in many disease states. It is recognized in the art that endothelial-cell specific receptor PTKs such as KDR and Tie-2 mediate the angiogenic process. In addition, many tyrosine kinases have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including hyperproliferative disorders. One skilled in the art would know that hyperproliferation and angiogenesis can be affected by inhibition of kinases.

Claims 37 and 38 are drawn to "affecting" hyperproliferative disorders and angiogenesis, respectively. To affect a disorder is not necessarily the same thing as curing the disorder. In fact, the effect does not even have to be a therapeutic effect, it merely has to have some sort of effect on the disorder. "Affect" can mean up-regulate or down-regulate.

The Examiner refers to In re Buting, 163 U.S.P.Q. 689 (C.C.P.A. 1969), in which clinical tests showing that a compound found to be useful in the treatment of two types of cancer was not found sufficient for a much broader range". The compounds of the present invention are linked by a common mechanism of action, and it is reasonable that such a mechanism may be exploited in a variety of diseases or disorders characterized by hyperproliferation or angiogenesis.

Therefore, the Examiner's rejection that Applicants have not met the statutory requirements of invention as defined by 35 U.S.C. §112, first paragraph is obviated and should be withdrawn.

Based upon the foregoing, Applicants believe that claims 18-21 and 23-45 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

Date: January 29, 2003

**Gayle B. O'Brien**
Agent for Applicants
Reg. No. 48,812

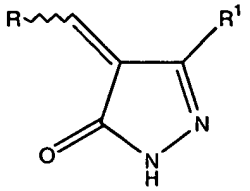
Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053

## APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

*In the claims:*

18. (Twice Amended) A compound represented by the following structural formula:




or physiologically acceptable salts thereof, wherein:

R is selected from the group consisting of substituted or unsubstituted: indolyl, imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzimidazolyl, 4,5,6,7-tetrahydroindolyl, benzoindolyl, azaindolyl, indazolyl, pyridinyl, quinolinyl, pyrimidinyl, phenyl, pyrazinyl, pyrrolyl, pyrazolyl, oxazolyl and thiazolyl;

$R^1$ is hydrogen or -A-Z;

A is $-(CH_2)_n-$, $-(CH_2)_nNH-$, $-(CH_2)_nO-$, $-(CH_2)_nS-$, $-(CH_2)_nS(O)-$ or $-(CH_2)_nS(O)_2-$;

Z is -H, a lower alkyl, aralkyl, trihalomethyl, trihalomethylcarbonyl, $R^3OC(O)-$, $-NR^4R^5$, $-C(O)NR^4R^5$, $R^3CO-$, $R^3O-$, or a ring system selected from the group consisting of a $C_3$-$C_6$ cycloalkyl, isoxazolyl, isothiazolyl, imidazolyl, phenyl, pyrrolyl, indolyl, pyridinyl, pyrazinyl, pyrimidinyl, benzothiazolyl, tetrahydrofuranyl, thiophenyl, imidazolyl, furanyl, triazinyl, benzimidazolyl, pyridazinyl, quinoxalinyl, pyrazolyl, oxazolyl, thiazolyl and the N-oxides thereof wherein said ring system can be optionally substituted with one or more moieties selected from the group consisting of halogens, lower alkyl, $R^3O-$, HO-, HOC(O)-, $R^3OC(O)-$, trihalomethyl, nitro, an aromatic group, a ($C_3$-$C_6$)cycloalkyl group, a heterocyclic group, an aralkyl group, a ($C_3$-$C_6$)cycloalkyl-alkyl group, a heterocyclyl-alkyl group, -CN, $-C(O)NR^4R^5$ or $-NR^4R^5$;

$R^3$ for each occurrence is, independently selected from the group consisting of substituted or unsubstituted: lower alkyl group, lower alkoxy lower alkyl group, aromatic group, ($C_3$-$C_6$)cycloalkyl group, heterocyclic group, aralkyl group, a ($C_3$-$C_6$)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

$R^4$ and $R^5$ for each occurrence are each, independently, hydrogen, or are selected from the group consisting of substituted or unsubstituted: lower alkyl group, aromatic group, ($C_3$-$C_6$)cycloalkyl group, heterocyclic group, aralkyl group, a ($C_3$-$C_6$)cycloalkyl-alkyl group, and heterocyclyl-alkyl group;

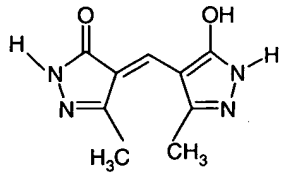
optionally, $R^4$ and $R^5$ together with the nitrogen to which they are attached represent morpholino, pyrrolidino, piperidino, imidazol-1-yl, piperazino, thiamorpholino, azepino or perhydro-1,4-diazepin-1-yl groups each optionally substituted by one or more moieties selected from the group consisting of lower alkyl, hydroxy, lower alkoxy lower alkyl, an aromatic group, a ($C_3$-$C_6$)cycloalkyl group, a heterocyclic group, an aralkyl group, a ($C_3$-$C_6$)cycloalkyl-alkyl group, and a heterocyclyl-alkyl group; and

n is an integer from 0 to 3;

provided that when R is an unsubstituted indol-3-yl then $R^1$ is not $-NH_2$;

and

provided that the compound is not




and

provided that when $R^1$ is methyl, R is not hydroxyphenyl, nitrophenyl, m-$OCH_3C_6H_4$, 4-hydroxy-3-methoxyphenyl or 2-hydroxy-3-bromophenyl.